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Multiple Sclerosis/Avonex

My disease of interest is multiple sclerosis and the drug that is currently being used against it is Avonex.

Multiple sclerosis is an autoimmune system where the body’s own immune system attacks the body of the individual. Multiple sclerosis targets the myelin sheath of the nerve cells slowing down the nerve impulses and ultimately stopping them, this is called inflammation. This disease occurs in more commonly in females than in males and it occurs around the age of 20 to 40, but can be see at any age. The cause of multiple sclerosis is still not known but theories state that viruses, genetic disorders, or even environmental factors cause it. People with a family history of multiple sclerosis have a higher risk of it.

A research article states the description of the drug target interferon alpha and beta receptors “A proposal is made that the IFN receptor, with its subunits IFNAR-1 and IFNAR-2, presents two separate ligand binding sites, and this double structure is both necessary and sufficient to ensure that the different IFN are recognized and can act selectively. The key feature is the duplication of the extracellular domain of the IFNAR-1 subunit and the configurational geometry that this imposes on the intracellular domains of the receptor subunits and their associated tyrosine kinases” (10).

Another article talks about the function of type 1 interferons (interferon beta-1a/Avonex) and their diverse pathways.“The functions of the type I IFN receptors have been elucidated with respect to ligand interaction, mechanisms of signal transduction, and biological responses. The pioneering studies that discovered IFNARs and their mechanisms of actions in vitro have been largely validated in vivo using gene targeted mice. This body of work has highlighted the important roles of IFNARs in mediating type I IFN responses in hematopoiesis and innate and acquired immunity to infection and cancer. However, IFNs elicit many biological effects that can even be opposite in different cell types. For example, type I IFN inhibits proliferation and is proapoptotic for many cell types, yet it prolongs the survival of memory T cells. The type I IFN receptor, typical of class II hCR, lack intrinsic kinase activity and thus rely on associated Janus kinases (JAKs) to phosphorylate receptors and signal transducing molecules, such as STAT proteins, after ligand-induced receptor clustering. IFNAR1 is preassociated with Tyk2, which also stabilizes IFNAR1 cell surface expression levels. The Tyk2 binding site on the huIFNAR1 cytoplasmic region has been localized to a region encompassing residues 479–511. HuIFNAR1 also bound STAT1 and STAT2 via phospho-Tyr466 and phospho-Tyr481 when overexpressed in heterologous cells. STAT3 reportedly undergoes a phosphotyrosine-dependent interaction with IFNAR1, consistent with STAT1 and STAT3 homo- and heterodimer formation after IFNα treatment.Using truncation mutants of the intracellular domain of huIFNAR2, the site of Jak1 binding was identified to a 47-aa region. Jak1, STAT1, and STAT2 may also be preassociated with IFNAR2. These data suggest that the intracellular domains and signal-transducing molecules such as STATs may form multimolecular signal transduction complexes in which each molecule has multiple interactions. Further diversity of IFNAR signaling is achieved by the activation of other pathways including other STAT proteins and non-STAT proteins. These ‘alternative’ signaling pathways include CrkL, Rap1, MAP kinases, Vav, RAC1, PI 3-kinase, IRS1 and -2, PMRT1, and Sin1” (7).

Interferon alpha and beta receptors have a molecular weight of 100-150 kD and are “highly expressed on potently peripheral blood B cells and monocytes” (11). Multiple sclerosis patients have high levels of type 1 interferons and the cause of this is plasmacytoid dendritic cells. Altougth interferon beta-1a is also a type 1 interferon when it is introduced to multiple sclerosis patients, “pDCs from IFN-beta-treated MS patients showed reduced expression of the pDC maturation markers CD83 and CD86 molecules” (9) which are antiviral responses when there are invaders like bacteria or viruses in the body, but in the case of multiple sclerosis it is expressed to destroy the bodies own cells in this case the myelin sheath. The body cannot distinguish self from nonself. This proves that interferon beta-1a affect the expression of plasmacytoid dendritic cells and the interferon beta-1a target interferon alpha and beta receptors (IFNAR) so IFNARs must be on the plasmacytoid dendritic cells as well.

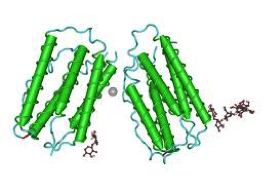
Avonex (Interferon beta-1a) is a 166 amino acid glycoprotein with a predicted molecular weight of approximately 22,500 daltons. It is produced by recombinant DNA technology using genetically engineered chinese hamster ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of Avonex is identical to that of natural human interferon beta-1a. It is basically a ligand that binds the interferon alpha and beta receptors in order to inhibit the antiviral proteins it produces. “The analysis also revealed that Avonex increased the number of dendritic cells producing interleukin-10, a protein that helps stop immune responses that may be harming myelin in multiple sclerosis” (11). Avonex is exactly the same as these proteins and they target the interferon beta and alpha receptors from the plasmacytoid dendritic cells in order to inhibit them from destroying the myelin sheath from the nerve cells. So the drug is targeting the cells that naturally produce type 1 interferons in order to modulate them. “These data indicate that IFN-beta modulates the immunologic functions of pDC, thus identifying pDCs as a novel target of IFN-beta therapy in MS patients” (9).

Avonex has been available since 1995 and Biogen Idec makes it. It is for everyone and is taken only once a week, which is why it is a highly popular drug. “Avonex has a specific activity of approximately 200 million international units (IU) of antiviral activity per mg of Interferon beta-1a determined specifically by an in vitro cytopathic effect bioassay using lung carcinoma cells (A549) and Encephalomyocarditis virus (ECM). Avonex 30 mcg contains approximately 6 million IU of antiviral activity using this method. The activity against other standards is not known. Comparison of the activity of Avonex with other Interferon betas is not appropriate, because of differences in the reference standards and assays used to measure activity” (3).

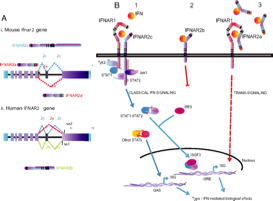
As with any other medicine distributed by the pharmaceutical industry, Avonex does contain side affects, but its effects vary with each individual. Avonex is somewhat effective for multiple sclerosis but it is not a cure. It only helps prevent the disease from occurring quickly for patients with relapsing-remitting multiple sclerosis. People with chronic progressive multiple sclerosis are at a loss with this drug because it has not been shown to help. Although this drug seems to have an effect on multiple sclerosis it is not known how it treats multiple sclerosis. Nursing mothers most chose between leaving Avonex or nursing because it the known what the drug does to the human milk. Safety and effectiveness of Avonex has not been evaluated for people below the age of 18. It is advisable for pregnant women to discontinue Avonex because the side effects of fetus development is not know. “In a 2 year pivotal study, Avonex slowed down physical disability progression by 37%. In a 5 year follow up to s separate study 90% of people taking Avonex were still active” (2). This information from the Avonex website suggests that Avonex is a highly effective treatment for multiple sclerosis but only for relapsing multiple sclerosis not chronic.

The mechanism of action for Avonex is “interferon beta binds to type I interferon receptors (IFNAR1 and IFNAR2c) which, upon dimerization, activate two Jak (Janus kinase) tyrosine kinases (Jak1 and Tyk2). These transphosphorylate themselves and phosphorylate the receptors. The phosphorylated INFAR receptors then bind to Stat1 and Stat2 (signal transducers and activators of transcription) which dimerize and activate multiple (~100) immunomodulatory and antiviral proteins. Interferon beta binds more stably to type I interferon receptors than interferon alpha” (8) It will take roughly around 33-55 L/hour with a healthy SC injection of 60 mcg for Avonex to clear out of the body system.

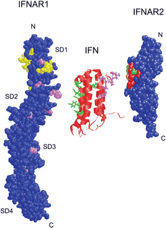
The molecular weight of Avonex is 22.5 kD, the CAS Registry Number is 145258-61-3, and the chemical formula for the drug is C908H1408N246O252S7. When searching for this information it is wise to search for interferon beta-1a instead of Avonex since it is the exact same thing. Interferon beta-1a will have more information than Avonex on the internet even though it is the same thing because it is a common scientific name. The following are pictures of interferon beta-1a (Avonex) binding with interferon alpha and beta receptors.



This is Avonex (interferon beta-1a) which is a type 1 interferon.



This is the binding of interferon beta-1a with the receptors and the pathways.



Another binding of interferon beta-1a and the interferon alpha and beta receptors.

The delivery method for Avonex is by injection. Side effects for Avonex are fever, shills, sweating, muscle aches, and tiredness (flue-like symptoms). The side effects affect each person differently, some may experience them and some may not. The scientific name for Avonex is interferon beta-1a as previously stated while some trade names are CinnoVex, Recigen, and Rebif and the maker of this drug is Biogen Idec. The patent is CA 1341604 so yes it is patented. There are 134 cases of clinical trials on clinicaltrials.gov and they are currently recruiting for multiple trials. A lot of the trials have been completed and some terminated. As previously stated this molecule is produced by recombinant DNA technology using genetically engineered chinese hamster ovary cells into which the human interferon beta gene has been introduced.

Some alternatives to Avonex are Rebif and Copaxone. Some consumers also complain that Avonex increases body fat. This drug is only known to help patients with multiple sclerosis not for anything else.

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